

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant:	Anthony Atala, et al.	
Application No.:	10/766,642-Conf. #4621	Group Art Unit: 1651
Filed:	January 28, 2004	Examiner: Allison M Ford
Entitled:	Enhancement Of Angiogenesis To Grafts Using Cells Engineered To Produce Growth Factors	
Docket No.:	105447-2	

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APPEAL BRIEF PURSUANT TO 37 C.F.R. § 41.37

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I. REAL PARTY IN INTEREST

The real party in interest is Wake Forest University Health Sciences of Winston-Salem, North Carolina, which derives its rights in this application by virtue of an assignment of the application by the inventors to Wake Forest University Health Sciences as recorded at Reel 022704 and Frame 0477.

II. RELATED APPEALS AND INTERFERENCES

None.

III. STATUS OF CLAIMS

Claims 1-4, 6-10, 12, 23-26, 28-29 and 33-37 are pending in the present application. Claims 5, 11, 13-22, 27 and 30-32 have been canceled. As of the December 23, 2008 Office Action, claims 1-4, 6-10, 12, 23-26, 28-29 and 33-37 stand twice rejected under 35 U.S.C. §103(a) in view of various combinations of cited art.

More specifically, with the December 23, 2008 Office Action, the Examiner again rejected claims 1-4, 6-10, 12, 23-26, 28-29 and 33-37 under 35 U.S.C. §103(a) as being unpatentable over US Patent Application 2003/0007954 to Naughton et al.; in view of US Patent 6,479,064 to Atala et al.; US Patent 6,692,738 to MacLaughlin et al.; J. Gene Med. vol. 2, page 279, 2000 to Springer et al.; Gene Therapy, vol. 8, page 523, 2001 to Rinsch et al.; and US Patent Application 2004/0161412 A1 to Penn et al. supported by 60/405,274 and 60/424,065.

Accordingly, claims 1-4, 6-10, 12, 23-26, 28-29 and 33-37 are subject to appeal.

IV. STATUS OF AMENDMENTS

No amendments have made subsequent to the Office Action mailed on December 23, 2008, and the Notice of Appeal submitted by the Appellants on March 23, 2009.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The current invention is directed to a method of organ augmentation that utilizes two populations of cells with distinct and separate functions, a *first population of cells* that is *encapsulated and transiently transfected* to express an *angiogenesis modulating agent*, and a *second population to be assimilated and differentiated* at the target site.

Independent claim 1 is directed to a method of organ augmentation comprising the steps of: *transiently transfecting a first population* of cells with a plasmid encoding the angiogenesis modulating agent VEGF, such that said first population of cells express VEGF for less than about 10 weeks; *encapsulating* the transfected first population of cells; selecting a *second population* of cells to be assimilated at a target tissue region upon implantation, wherein the second population of cells comprises *myoblasts*; suspending the encapsulated first population of cells and the second population of cells in an *injectable polymer matrix*; injecting the encapsulated first population of cells and the second population of cells and the polymer matrix into the target tissue region where the encapsulated first population of cells will express the VEGF angiogenesis modulating agent, thereby *inducing assimilation and differentiation of the myoblasts in the target region* and augmenting organ function. [Submitted application page 2, line 23; page 3, lines 2, 6-8 and 32; page 19, line 14; page 31, line 23; and page 35, lines 1-4.]

Independent claim 23 is directed to a method for augmenting organ function comprising: *transiently transfecting a first population of cells* with a plasmid encoding an *angiogenesis modulating agent*; *encapsulating* the transfected first population of cells; culturing at least a second population of cells *on a matrix material* to produce an organ construct, wherein the second population of cells comprises cells of a different cell type than the first population, and either the first or second population of cells comprises myoblasts; and *implanting* the organ construct and the encapsulated first population of cells *in vivo* at one target site to replace or augment organ function, such that the encapsulated first population of cells express the angiogenesis modulating agent for less than about 3 weeks and the second population of cells assimilate and differentiate at the target site. [Submitted application page 3, lines 2, 6-8 and 32; page 4, line 20; page 5, line 24; page 6, line 6; page 19, line 14; page 32, line 5; and page 35, lines 1-4.]

Appellants' dependent claims each recite more particular configurations of the claimed constructs. Claims 2-4, 6-10 and 12 recite particular aspects of the method of organ augmentation with an injectable polymer matrix. Claims 24-26, 28-29 and 33-37 recite particular aspects of the method of organ augmentation with an organ construct.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Whether the Examiner improperly rejected claims 1-4, 6-10, 12, 23-26, 28-29 and 33-37 pursuant to 35 U.S.C. §103(a) as being obvious over US Patent Application 2003/0007954 to Naughton et al.; in view of US Patent 6,479,064 to Atala et al.; US Patent 6,692,738 to MacLaughlin et al.; J. Gene Med. vol. 2, page 279, 2000 to Springer et al.; Gene Therapy, vol. 8, page 523, 2001 to Rinsch et al.; and US Patent Application 2004/0161412 A1 to Penn et al. supported by 60/405,274 and 60/424,065.

VII. ARGUMENT

A. The Examiner improperly rejected claims 1-4, 6-10, 12, 23-26, 28-29 and 33-37 pursuant to 35 U.S.C. §103(a) as being obvious over US Patent Application 2003/0007954 to Naughton et al.; in view of US Patent 6,479,064 to Atala et al.; US Patent 6,692,738 to MacLaughlin et al.; J. Gene Med. vol. 2, page 279, 2000 to Springer et al.; Gene Therapy, vol. 8, page 523, 2001 to Rinsch et al.; and US Patent Application 2004/0161412 A1 to Penn et al. supported by 60/405,274 and 60/424,065.

1. The Examiner's Rejections and the Scope and Content of the Prior Art

The Examiner rejects claims 1-4, 6-10, 12, 23-26, 28-29 and 33-37 pursuant to 35 U.S.C. §103(a) as being obvious over US Patent Application 2003/0007954 to Naughton et al.; in view of US Patent 6,479,064 to Atala et al.; US Patent 6,692,738 to MacLaughlin et al.; J. Gene Med. vol. 2, page 279, 2000 to Springer et al.; Gene Therapy, vol. 8, page 523, 2001 to Rinsch et al.; and US Patent Application 2004/0161412 A1 to Penn et al. supported by 60/405,274 and 60/424,065 stating:

"At the time the invention was made the need for effective methods of reconstructing and repairing ischemic tissues was well recognized in the art (See, e.g. Naughton et al, page 1). It is the opinion of the Office that Applicants' currently claimed methods are a combination of several treatment methods which were each taught in the prior art."

Naughton et al. (2003/0007954) teach a three-dimensional stromal tissue implant. In the reference, stromal cells are grown on a biocompatible structure or framework and the implant is used for attachment to various locations. However, Naughton et al. fail to teach a method comprising the combination of two separate populations of cells, where a first population is transiently transfected and encapsulated to express VEGF and a second population is implanted in a polymer matrix or organ construct to assimilate and differentiate at a target site.

The Examiner cites Atala et al., MacLaughlin et al., Springer et al., Rinsch et al., and Penn et al. to support Naughton et al. and teach various matrix materials and forms and types of cells.

More specifically, the Examiner states that Atala et al. and MacLaughlin et al. teach "various substrate materials and forms could be successfully utilized for delivery of cells to a target issue region" and the "inclusion of vascular endothelial cells, in addition to stromal/parenchymal cells, in tissue engineered constructs was known." Atala et al. describe how to prepare artificial organ constructs from decellularized scaffold matrices seeded with endothelial cells. MacLaughlin et al. describe implantable tissue matrices seeded with genetically engineered cells.

Furthermore, the Examiner cites Springer et al. and Rinsch et al. Springer et al. teach capsules containing VEGF expressing myoblasts. Rinsch et al. teach encapsulation of genetically engineered myoblasts to express VEGF or FGF-2.

Lastly, Examiner cites Penn et al. to teach methods of transiently expressing angiogenesis modulating gene(s). Penn et al. teach transfecting myoblasts with VEGF to induce VEGF expression in ischemic tissue

The Examiner further stated on page 4 of the Office Action that "none of the references were applied as anticipatory, but rather were relied upon in combination, as no one reference was

submitted to disclose all of the claimed limitations.” Moreover, on page 10 of the Office Action the Examiner stated that:

combining the therapies of implanting new engineered tissue to sites of ischemic tissue (disclosed by Naughton et al) and delivering microcapsules containing cells genetically engineered to transiently express angiogenesis modulating agents to sites of ischemic tissue (disclosed by Springer et al and Rinsch et al, taken in view of Penn et al) into a single method would have been obvious.

2. No Motivation to Modify Naughton

The Examiner stated in the Office Action dated December 23, 2008, that the requirement for a “recognition of a deficiency in the art and an explicit motivation to modify or combine prior art teachings is not the standard for proper rejection under 35 USC 103(a).” However in order to satisfy the burden of obviousness in light of combination, as explained in *KSR International Co. v. Teleflex, Inc.*, “rejections on obviousness cannot be sustained with mere conclusory statements; instead, there *must be some articulated reasoning with some rational underpinning* to support the legal conclusion of obviousness.” (MPEP § 2142, citing *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006); emphasis added; *see also* MPEP § 2143.01.) It is not enough to pick and choose features from various pieces of art and just combine them to arrive at the claimed invention without any support for making such combinations. (*In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596 (Fed. Cir. 1988).) The Board must guard against impermissible hindsight obtained from the knowledge of the invention of the present application and the Examiner may not “use the claimed invention as an instruction manual or ‘template’ to piece together the teachings of the prior art so that the claimed invention is rendered obvious.” (*In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (citation omitted).)

Here the Examiner has not articulated any reason to combine Naughton et al. with the secondary references of *Atala et al.*, *MacLaughlin et al.*, *Springer et al.*, *Rinsch et al.* and *Penn et al.* Specifically, there is no suggestion that the Naughton et al. reference is unsatisfactory, and there stands no motivation for one of ordinary skill in the art with knowledge of Naughton et al. to search for a method of organ augmentation as disclosed in the current invention. The statement that “the need for effective methods of reconstructing and repairing ischemic tissue is well known in the art” is not a reason to combine the references; it is merely a description of the

problem that the invention addresses.

Moreover, the only apparent reason for the combination suggested by the Examiner is because Appellants' teachings serve as a guide: "[A]pplicants' currently claimed methods are a combination of several treatment methods which were each taught in the art." Again, this is not an articulated reason to combine the cited references and certainly not the proper standard since virtually every invention can be seen as a combination of previously known components.

It is improper to pick and choose features from the prior art in such a manner. Recently, the Federal Circuit concluded in *Ortho McNeil Pharmaceutical, Inc. v. Mylan Laboratories*, No. 2007-1223 (March 31, 2008), that the reasoning of "simply retrac[ing] the path of the inventor with hindsight, discount[ing] the number and complexity of the alternatives, and conclud[ing] that the invention was obvious ... is always inappropriate for an obviousness test." Furthermore, "the inventor's insights, willingness to confront and overcome obstacles, and yes, even serendipity, cannot be discounted."

The present rejection is an exemplary illustration of a situation in which the Examiner is relying on the present invention as an instruction manual or "template" to piece together various disclosures from the prior art to arrive at the claimed invention. The Examiner cites six different references (Naughton, MacLaughlin, Atala, Springer, Rinsch and Penn) to arrive at the present invention. The Examiner starts with Naughton et al, and then based on the teachings of the present invention, bits and pieces from each of the other references to arrive at the present invention. In fact, the Examiner requires at least two prior art references to reconstruct a population similar to the second population of the invention transplanted either in an injectable matrix or in an organ construct (Naughton et al with MacLaughlin et al or Naughton et al with Atala et al). Likewise, no less than three prior art references are required to reconstruct similar steps to the Appellants' steps of transiently transfecting a first population of cells with VEGF and encapsulation (see Springer et al, Rinsch et al and Penn et al).

With particular reference to the teachings of Naughton et al, no person having ordinary skill in the art, in view of Atala et al, MacLaughlin et al, Springer et al, Rinsch et al and Penn et al, would have a reason for making the Examiner's proposed combination or would have made the combination at the time of the Appellants' invention.

The Examiner also fails to take into consideration the complexities of the current invention. The steps of transiently transfecting a first population of cells with VEGF and encapsulation produces a population of cells protected from the host's immune system while capable of transiently expressing an angiogenesis modulating agent to promote the assimilation and differentiation of the second population of cells comprising myoblasts. The steps of coinjecting the second population with the encapsulated first population in an injectable matrix or culturing the second population on a matrix to produce an organ construct and implanting the organ construct together with the encapsulated first population both improve vascularization and organ augmentation.

3. Claims 1-4, 6-10, 12, 23-26, 28-29 and 33-37 Are Not Obvious Over Naughton; in view of Atala; MacLaughlin; Springer; Rinsch; and Penn

Furthermore, the Appellants' note that in addition to the inappropriate nature of the obviousness rejection, the combination of references cited by the Examiner does not disclose all the claimed limitations of the invention. The Examiner even stated in the Office Action that "no one reference was submitted to disclose all the claimed limitations."

Naughton (2003/0007954) teaches a three-dimensional stromal tissue implant. In the reference, stromal cells are grown on a biocompatible structure or framework and the implant is used for attachment to various locations. Atala et al. describe how to prepare artificial organ constructs from decellularized scaffold whole tissue matrices seeded with endothelial cells to replace organs. MacLaughlin et al. describe implantable tissue matrices seeded with genetically engineered cells. Springer et al. teach capsules containing VEGF expressing myoblasts. Rinsch et al. teach encapsulation of genetically engineered myoblasts to express VEGF or FGF-2 and Penn et al. teach transfecting myoblasts with VEGF to induce VEGF expression in ischemic tissue. Combining all the references does not reconstruct the claimed invention of the current application that is directed to a method comprising the steps of *transiently transfecting a first population of cells* to express an angiogenesis modulating agent and *encapsulating the transfecting first population of cells* and then combining such encapsulated *first population of*

cells with a *second population* of cells to be assimilated and differentiated at a target site in an injectable polymer matrix as in claim 1 or part of an organ construct as in claim 23.

In fact, none of the cited references, alone or in combination, teach or suggest the invention as a whole, much less a method comprising two separate populations of cells, where a first population is transiently transfected and encapsulated to express VEGF and a second population is implanted in a polymer matrix or organ construct to assimilate and differentiate at a target site. Furthermore, combining all the references does not reconstruct the claimed invention that is directed to a method comprising the steps of *transiently transfecting a first population of cells* to express an angiogenesis modulating agent and *encapsulating the transfected first population of cells* and then combining such encapsulated *first population of cells* with a *second population* of cells to be assimilated and differentiated at a target site in an injectable polymer matrix as in claim 1 or part of an organ construct as in claim 23.

VIII. CONCLUSION

In summary, claims 1-4, 6-10, 12, 23-26, 28-29 and 33-37 are not obvious. Claims 1-4, 6-10, 12, 23-26, 28-29 and 33-37 are patentable because no combination of the cited references discloses or suggests the claimed invention. Moreover, Appellants submit that the pending claims define patentable subject matter. Accordingly, Appellants respectfully request that the Examiner's rejection of these claims be reversed and that the pending application be passed to issue.

Respectfully submitted,

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APPENDIX A: CLAIMS ON APPEAL

1. (Previously Presented) A method of organ augmentation comprising the steps of:
 - transiently transfecting a first population of cells with a plasmid encoding the angiogenesis modulating agent VEGF, such that said first population of cells express VEGF for less than about 10 weeks;
 - encapsulating the transfected first population of cells;
 - selecting a second population of cells to be assimilated at a target tissue region upon implantation, wherein the second population of cells comprises myoblasts,
 - suspending the encapsulated first population of cells and the second population of cells in an injectable polymer matrix;
 - injecting the encapsulated first population of cells and the second population of cells and the polymer matrix into the target tissue region where the encapsulated first population of cells will express the VEGF angiogenesis modulating agent, thereby inducing assimilation and differentiation of the myoblasts in the target region and augmenting organ function.
2. (Previously Presented) The method of claim 1, wherein the step of transfecting the first population of cells comprises transiently transfecting the cells such that the angiogenesis modulating agent is produced for less than three weeks.
3. (Previously Presented) The method of claim 1, wherein the first population of cells comprises undifferentiated cells.
4. (Previously Presented) The method of claim 1, wherein the first population of cells comprises vascular endothelial cells (EC).
5. (Canceled)
6. (Previously Presented) The method of claim 1, wherein the second population of cells comprises undifferentiated cells.
7. (Previously Presented) The method of claim 1, wherein the second population of cells comprises vascular endothelial cells (EC).

8. (Previously Presented) The method of claim 1, wherein the polymer matrix comprises collagen.
9. (Previously Presented) The method of claim 8, wherein the polymer matrix comprises collagen type I.
10. (Previously Presented) The method of claim 1, wherein the encapsulated first population of cells express the VEGF angiogenesis modulating agent for less than about three weeks.
11. (Canceled)
12. (Previously Presented) The method of claim 1, wherein the first population of cells comprises myoblasts.
13. – 22. (Canceled)
23. (Previously Presented) A method for augmenting organ function comprising:
 - transiently transfecting a first population of cells with a plasmid encoding an angiogenesis modulating agent;
 - encapsulating the transfected first population of cells;
 - culturing at least a second population of cells on a matrix material to produce an organ construct, wherein the second population of cells comprises cells of a different cell type than the first population, and either the first or second population of cells comprises myoblasts; and
 - implanting the organ construct and the encapsulated first population of cells *in vivo* at one target site to replace or augment organ function, such that the encapsulated first population of cells express the angiogenesis modulating agent for less than about 3 weeks and the second population of cells assimilate and differentiate at the target site.
24. (Original) The method of claim 23, wherein the matrix is decellularized tissue.
25. (Original) The method of claim 23, wherein the matrix is a hydrogel.
26. (Original) The method of claim 23, wherein the matrix is a polymer.

27. (Canceled)
28. (Original) The method of claim 23, wherein the angiogenesis modulating agent is VEGF.
29. (Previously Presented) The method of claim 23, wherein the method further comprises assimilating the encapsulated first population of cells into a tissue layer.
- 30.-32. (Canceled)
33. (Previously Presented) The method of claim 23, wherein the organ construct and the encapsulated first population of cells are each implanted *in vivo* at a plurality of target sites.
34. (Previously Presented) The method of claim 1, wherein the step of encapsulating the transfected first population of cells further comprises using microspheres.
35. (Previously Presented) The method of claim 1, wherein the step of encapsulating the transfected first population of cells further comprises using alginate-PLL capsules.
36. (Previously Presented) The method of claim 23, wherein the step of encapsulating the transfected first population of cells further comprises using microspheres.
37. (Previously Presented) The method of claim 23, wherein the step of encapsulating the transfected first population of cells further comprises using alginate-PLL capsules.

APPENDIX B: EVIDENCE

None.

APPENDIX C: RELATED PROCEEDINGS

None.

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